Letter to the Editor

Clinical Cancer Research

Exercise Window Trial in Newly Diagnosed Breast Cancer–Letter

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We read with great interest the article by Ligibel and colleagues (1), of the Pre-Operative Health and Body (PreHAB) study looking at the molecular effects of exercise on breast tumors between diagnosis and surgery. The reported upregulation of pathways related to inflammation and immunity is consistent with the expected role of the tumor microenvironment in response to exercise (2). Sequentially sampled window studies have great potential to inform by minimizing patient–patient variation, but are a very challenging way to examine the effects of treatment or other interventions. Assessment of proliferation is a natural endpoint for response, but measurement of Ki67 is notoriously unreliable.

There are many different gene expression analysis approaches and numerous breast cancer signatures (3). The current drive for reproducible research has led to expectations that datasets and analysis software are made freely available. With this in mind and our desire to perform similar studies, we reanalyzed the PreHAB study gene expression data (GSE129508) using the GeneFu package (4) to calculate estimations of the established genomic grade index, PAM50 and Mammaprint risk of relapse prognosis prediction algorithms of the samples taken at diagnosis and excision from patients randomized to the exercise and control groups.

The majority of exercising patients (12/16) had significantly reduced predicted PAM50 risk of relapse scores ($P = 0.03$), whereas half of the control group had smaller nonsignificant ($P = 0.81$) reductions in predicted risk of relapse. Trends ($P = 0.08$ and $P = 0.09$) for reductions in genomic grade index and Mammaprint scores in most exercising patients were not evident in controls (Fig. 1). These prognostic signatures were derived from different analytic approaches and represent different facets of breast tumor biology including proliferation, immune response, and estrogen signaling.

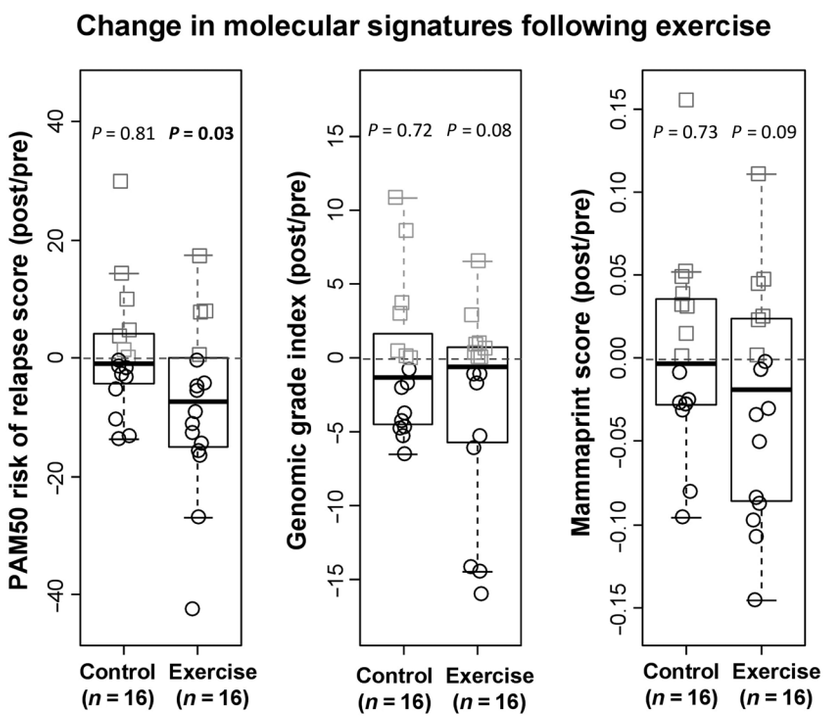

Figure 1.
Presurgical exercise improves predicted prognosis for patients with breast cancer. Reductions in molecular signature scores are shown as black circles and increases as gray squares.

Whole-tumor gene expression profiling captures information on all cell types, whereas deconvolution approaches can generate *in silico* predictions of the proportions of immune cell types present in samples. As above, we used the ImSig package (5) to assess changes in immune cell content changes in the PreHAB

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data. Increases in several immune cell types were observed including macrophages and B cells, alongside a reduction in proliferation, but these changes were not statistically significant.

Our analysis highlights different analysis approaches and supports the findings of the original study. We strongly encourage further studies in this area to examine the biological consequences of exercise on tumors along with assessments of the feasibility of introducing optimal and tolerable exercise regimens into routine clinical care for patients with cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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